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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,304	02/21/2001	Christopher Silvia	018512-00041	3840

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/23/2002 16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,304	SILVIA ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 7, 16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-9, drawn to an isolated nucleic acid encoding a polypeptide monomer in Paper No. 15 (31 July 2002) is acknowledged. The traversal is on the ground(s) that the groups set forth by the Examiner all stem from a common concept and theory and involve related compounds and methods. Applicant also indicates that the prosecution of the claims of Groups I-VIII would not place a substantially greater burden on the Examiner. This is not found persuasive because as discussed in the previous Office Action (Paper No. 14, 28 June 2002), Groups I-VIII constitute different products and methods which are patentably distinct inventions. The products of Groups I-III and VIII are structurally and functionally different from one another. Additionally, the methods of Groups IV-VII require different ingredients, process steps, and endpoints. Each invention is unique, requiring a unique search of the prior art. Searching all of the inventions in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15 (31 July 2002).

Claims 1-9 are under consideration in the instant application.

Sequence Compliance

The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (Paper No. 12, 23 April 2002) has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply (Paper Nos. 9 and 11, 31 December 2001 and 22 March 2002) are withdrawn.

Information Disclosure Statement

The information disclosure statement filed 06 August 2001 (Paper No. 6) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Specification

1. The disclosure is objected to because of the following informalities:

2. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a 371 of PCT/US99/04549, filed March 2, 1999 and claims priority to U.S. provisional Application No. 60/076,621, filed March 3, 1998" should be entered.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 19, line 18). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "NUCLEIC ACID ENCODING HUMAN KIR51.".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, claims 1-9 are directed to an isolated nucleic acid encoding a polypeptide monomer comprising an alpha subunit of a potassium channel, the polypeptide monomer (i) forming with at least one additional Kir alpha subunit, a potassium channel having the characteristic of inward rectification, (ii) having a monomer tail region that has greater than 80% amino acid sequence identity to Kir5.1 tail region and (iii) specifically binding to polyclonal antibodies generated against SEQ ID NO: 1. The claims also recite a nucleic acid that encodes human Kir5.1, a nucleic acid that encodes SEQ ID NO:1, and a nucleic acid that has a nucleotide sequence of SEQ ID NO: 2. The claims recite that the nucleic acid encodes a polypeptide monomer having a molecular weight of about between 38kDa to 48kDa and a nucleic acid that

encodes a polypeptide monomer that specifically hybridizes under stringent conditions to SEQ ID NO: 2.

The specification asserts that the human Kir5.1 polypeptide (SEQ ID NO: 1) encoded by the claimed nucleic acid (SEQ ID NO: 2) of the present invention is an inward rectifier potassium channel. The specification teaches that inward rectifier channels mainly allow potassium influx, with little potassium outflux and have significant roles in maintaining the resting potential and in controlling excitability (pg 2, lines 27-28; pg 6, lines 24-25). However, the instant specification does not teach any significance or functional characteristics of the human polynucleotide (SEQ ID NO: 2) or polypeptide (SEQ ID NO: 1). The specification also does not disclose any methods or working examples that indicate the polynucleotide and polypeptide of the instant invention are involved in potassium flow in a cell. Since significant further research would be required of the skilled artisan to determine how the claimed polypeptide is involved with the above-mentioned activities, the asserted utilities are not substantial. The specification asserts the following as patentable utilities for the claimed putative polynucleotide (SEQ ID NO: 2):

1) to produce antibodies against the polypeptides (pg 32-34)

2) to identify and test for modulators, inhibitors, and activators of channels comprising hKir5.1 (pg 9, lines 13-17; pg 40-42)

3) to screen libraries of therapeutic compounds to identify those which specifically bind the polypeptide (pg 42-44)

4) to demonstrate its ability of form heteromeric potassium channels with inward rectifier activity (pg 57, lines 19-28)

5) in tissue typing (pg 58)

Each of these shall be addressed in turn.

1) to produce antibodies against the polypeptides. This asserted utility is credible but not specific or substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptides, therefore both polypeptides and their antibodies have no patentable utility. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) to identify and test for modulators, inhibitors, and activators of channels comprising hKir5.1. This asserted utility is credible but not specific or substantial. Such assays can be performed with any polypeptide. However, the specification discloses nothing specific or substantial for the modulators, inhibitors, or activators that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) to screen libraries of therapeutic compounds to identify those which specifically bind the polypeptide. This asserted utility is credible, but not specific or substantial. Such assays can be performed with any polypeptide. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to demonstrate its ability to form heteromeric potassium channels with inward rectifier activity. The specification teaches that 1:1 mixtures of hKir5.1 and hKir4.1 or cells expressing a tandem dimer of hKir5.1 and hKir4.1 show greater fluorescent dye changes than do cells expressing hKir5.1 alone (pg 57 and Figure 1). However, the specification does not

disclose an absolute negative control wherein the sample cells do not contain either Kir5.1 or Kir4.1. It cannot be determined from Figure 1 if the cells expressing hKir5.1 alone would have a current magnitude significantly larger than control cells not expressing the channel. Although this asserted utility is credible, it is not specific because such assays can be performed with any polypeptide. Furthermore, since the skilled artisan would not readily use the claimed polypeptide to form a heteromeric potassium channel because the protein has not been shown to have an increased current magnitude compared to control, the asserted utility is not substantial.

5) in tissue typing. The specification of the instant application teaches that hKir5.1 is expressed in various tissues, including pancreas, thyroid gland, salivary gland, and kidney (pg 58). However, the asserted patentable utility of tissue typing for the claimed hKir5.1 is not substantial because one skilled in the art would not readily use the protein in tissue-typing in a real world sense since the protein is not specific to one tissue and is not associated with any disease or disorder. Furthermore, this asserted utility is not specific because numerous unrelated proteins would also show a similar tissue typing pattern. Also, evidence of mere expression in a tissue is not tantamount to a showing of a role in hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency.

6. Claims 1-9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, claims 1-7 and 9 recite an isolated nucleic acid encoding a polypeptide monomer wherein the polypeptide monomer has a monomer tail region that has greater than 80% amino acid sequence identity to a human Kir5.1 tail region.

The specification teaches that identification of polymorphic variants and alleles of hKir5.1 is made by comprising the amino acid sequence of the tail region (approximately amino acids 352-384 of hKir5.1 of SEQ ID NO: 1). The specification also discloses that "amino acid identity of approximately at least 60% or above, preferably 80%, most preferably 90-95% or above in the tail region typically demonstrates that a protein is a polymorphic variant or allele of hKir5.1" (pg 8, lines 19-24). However, the specification does not teach nucleic acid variants or polypeptide variants. Further, the specification does not teach any functional or structural characteristics of the nucleic acid of SEQ ID NO: 2 or the polypeptide of SEQ ID NO: 1 or variants thereof.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in

underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the polynucleotide of SEQ ID NO: 2 to make a biologically active human Kir5.1 without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

Further, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. For example, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such

amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations and also embrace a broad

class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 and 9 recite an isolated nucleic acid encoding a polypeptide monomer wherein the polypeptide monomer has a monomer tail region that has greater than 80% amino acid sequence identity to a human Kir5.1 tail region.

The specification teaches that identification of polymorphic variants and alleles of hKir5.1 is made by comprising the amino acid sequence of the tail region (approximately amino acids 352-384 of hKir5.1 of SEQ ID NO: 1). The specification also discloses that "amino acid identity of approximately at least 60% or above, preferably 80%, most preferably 90-95% or above in the tail region typically demonstrates that a protein is a polymorphic variant or allele of hKir5.1" (pg 8, lines 19-24). However, the specification does not teach nucleic acid variants or polypeptide variants. Further, the specification does not teach any functional or structural characteristics of the nucleic acid of SEQ ID NO: 2 or the polypeptide of SEQ ID NO: 1 or variants thereof. The description of one hKir5.1 polynucleotide species (SEQ ID NO: 2) and one hKir5.1 polypeptide species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants

and fragments of a nucleic acid molecule encoding a polypeptide monomer having a monomer tail region that has greater than 80% amino acid sequence to a human Kir5.1 tail region.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule encoding a polypeptide monomer having a monomer tail region that is identical to a human Kir5.1 tail region, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 6 is rejected as being vague and indefinite for omitting the method by which the molecular weight is calculated that determines the numerical value of a polypeptide monomer.

10. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions of **A** X SSC and **B** % SDS at **C**°C"), claims 8-9 fail to define the metes and bounds of the varying structures of polynucleotides recited.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Bond et al. FEBS Letters367 : 61-66, 1995.

Pessia et al. J Physiol 532(2) : 359-367, 2001.

Tanemoto et al. J Physiol 525(3) : 587-592, 2000.

Tucker et al. J Biol Chem 275(22): 16404-16407, 2000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
October 17, 2002

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600